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Crystal Water Molecules and Solvation Effects on Protein-Ligand Docking

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In this report, we briefly present our recent study which investigates the influence of solvation energies and of crystal water molecules on the ligand binding orientation and affinity. Recently, we integrated fully movable water molecules into our docking program *FlexScreen*. These water molecules have translational and rotational degrees of freedom and if their presence is very unfavorable at a protein-ligand conformation, they are not considered at all. Additionally, we present our progress in improving our scoring function by incorporating into the function the solvation energies of the protein-ligand complex. The solvation energies are also calculated during the docking simulation itself.

1 Methods

A high-throughput in-silico screening method like *FlexScreen* consists of three major elements: (1) a *suitable virtual representation* of existing protein-ligand systems, (2) a *scoring function* that approximates the binding energy (ideally the affinity) of the protein-ligand complex as a function of the conformation of this complex[1,2] and (3) an efficient *optimization method* that is able to locate the best protein-ligand conformation on the potential energy surface[3,4]. In this report, we present our progress in points (1) and (2). So far, we have already developed a simulation approach that allows the protein structure to adapt to the docking ligand by conformational changes in the side chains. This approach has proved to be successful and results in more accurate and reliable database screens than an approach using only one rigid protein structure for the simulations[2].

1.1 Crystal Water Molecules

An additional important aspect is the influence of water molecules on the ligand binding affinity and on the ligand binding orientation. Firstly, we focus on the influence of crystal water molecules. These water molecules are strongly stabilized in the hydrogen bond network of the protein and therefore are well preserved in the crystal structures obtained by X-ray diffraction patterns. Secondly, solvation effects are considered in sec. 1.2.
When a ligand binds to a protein, it pushes aside water molecules in the protein cavity. As a consequence, a part of the water molecules are removed into the bulk solvent whereas others are involved in the stabilization of the ligand binding orientation. The spatial distribution of crystal water molecules in the protein cavity differs for bound ligands. Using one of those distributions as a fixed element in docking simulations, prevents many other high-affinity ligands from binding. Because of this and the already large conformational protein-ligand space, changeable water molecules are usually neglected for simulations.
In the following, we report our progress and our methodology for docking simulations

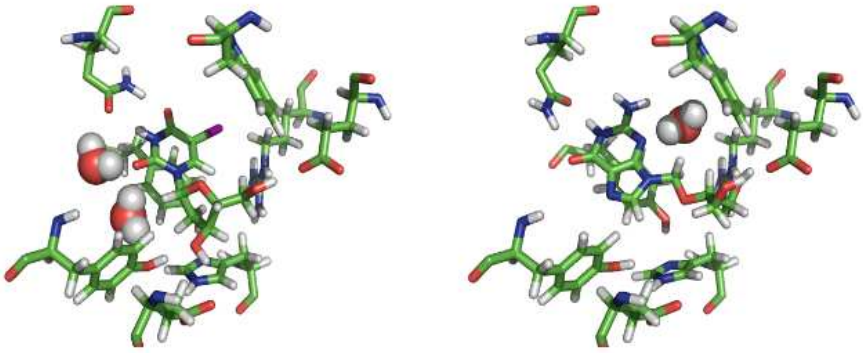

Figure 1. Illustration of two docking simulations with three additional flexible water molecules. Left picture: binding conformation of the ligand idu with the protein thymidine kinase (TK). Right picture: binding conformation of the ligand gcv with TK.

with flexible and movable water molecules in the protein cavity. Before docking, we select flexible water water molecules which have the degrees of freedom of translation, rotation and of moving into the solvent, if unfavorable. We performed docking simulations with the ligand gcv and idu to the protein thymidine kinase (TK). Figure 1 illustrates both resulting binding conformations with our new methodology. In the left picture of figure 1, the ligand idu is stabilized by two water molecules, whereas in the right picture the ligand gcv is bound to only one crystal water molecule. Our new methodology has the advantage that water molecules may actively stabilize a ligand conformation with their updated orientation. At the same time ligands are not hindered from binding.

1.2 Solvation Effects

The hydrophilic and hydrophobic properties of a ligand do not only influence the binding affinity, but also the binding orientation in protein pockets accessible to the bulk solvent. In the *FlexScreen* scoring-function we approximate the solvation energies through an implicit solvation model by calculating the solvent accessible surface areas of each atom (SASA)[5]

$$E_{Solvation} = \sum_i \gamma_i A_i^{\mathrm{SASA}}, \tag{1}$$

A_i^{SASA} being the solvent accessible surface area of atom i and γ_i the proportional factor of the atom type of atom i that relates the surface area to solvation energies. Considering these contributions during a simulation enables us to also reliably predict the binding orientations in open protein pockets. Figure 2 illustrates the consequences of neglecting and of considering the solvation effects, described with eq. 1. Docking conformations close to the native conformations can only be stabilized by taking solvation energies into account. As a consequence, methods like the thermodynamic cycle approach[6] can not be applied here. This method is only applicable, if the final protein-ligand conformation is independent of simulations being in vacuum or in solution.

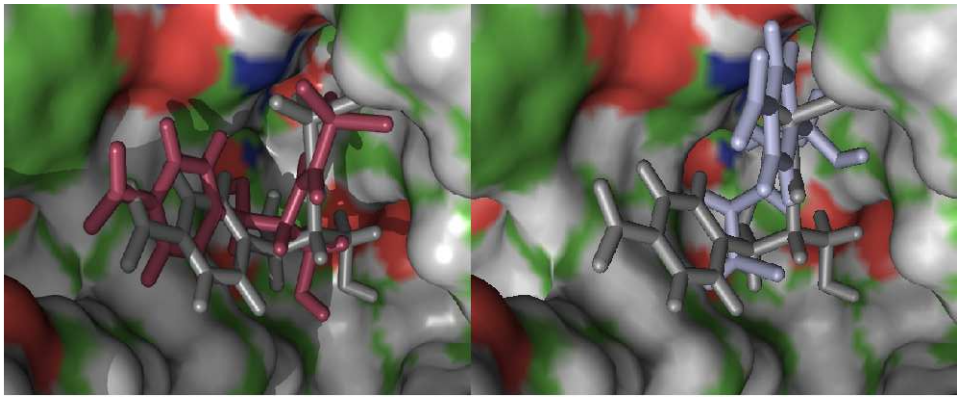

Figure 2. Comparing *FlexScreen* docking results with the experimental binding mode of the protein-ligand complex 3cla (pdb-code). The native ligand conformation is colored grey. Left picture: solvation effects are not considered and the simulation fails to predict the native binding mode. Right picture: solvation effects are included and the experimental binding conformation can be reproduced.

2 Conclusion

Crystal water molecules and water molecules from the bulk solvent sometimes have to be considered during docking simulations itself. With our approach we have started to study the effects these water molecules have. Larger quantitative studies are still missing and further work has also to be done to refine the parameters for the SASA-solvation energies.

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